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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte IVAN C. KING and LI-MOU ZHENG

Appeal 2009-014775
Application 10/738,423
Technology Center 1600

Before TONI R. SCHEINER, MELANIE L. McCOLLUM, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

McCOLLUM, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a cancer treatment method. The Examiner has rejected the claims on appeal as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

Claims 113, 115-117, and 119-124 are on appeal (App. Br.[2] 4). Claims 118 and 125 are also pending but have been withdrawn from consideration by the Examiner (Final Rej. 2-3).[3]

We will focus on claims 113, 115, and 123, which read as follows:

113. A method of inhibiting the growth of, or reducing the volume of a solid tumor cancer, comprising administering to a subject having a solid tumor cancer an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted *Salmonella,* wherein the *Salmonella* comprises an msbB$^-$ mutant.

115. The method of claim 113 wherein, the solid tumor or cancer is either a lung cancer or colon cancer.

123. A method of inhibiting the growth of, or reducing the volume of a solid tumor cancer, comprising administering to a subject having a solid tumor cancer an effective amount of,

(a) a pharmaceutical composition consisting essentially of an anti-cancer compound and one or more pharmaceutically acceptable carriers, and

(b) an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises an msbB$^-$ mutant.

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[2] As used herein, "App. Br." refers to the Response to Notification of Non-Compliant Appeal Brief dated January 9, 2009. In addition, "Final Rej." refers to the Final Rejection dated December 20, 2007; "Ans." refers to the Examiner's Answer dated February 5, 2009; "Reply Br." refers to the Reply Brief dated March 12, 2009; "Supp. Ans." refers to the Supplemental Examiner's Answer dated May 11, 2009; and "2d Reply Br." refers to the Reply Brief dated June 29, 2009.

[3] Appellants filed an Amendment canceling claims 122-125 on June 29, 2009. However, the Examiner has not indicated whether this Amendment had been entered. Thus, we include these claims in our decision.

The other claims on appeal have been argued with and therefore stand or fall with claims 113, 115, or 123. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on the following references:

K. Brooks Low et al., *Lipid A mutant Salmonella with suppressed virulence of TNFα induction retain tumor-targeting in vivo*, 17 NAT. BIOTECH. 37-41 (1999) (hereinafter "Low").

J. Schachter et al., *A Sequential Four-drug Chemotherapy and Biotherapy with Interferon Alpha and GM-CSF – An Innovative Protocol for the Treatment of Metastatic Melanoma*, 13 CANCER BIOTHER. RADIOPHARM. 155-164 (1998) (hereinafter "Schachter").

John M. Pawelek et al., *Tumor-targeted Salmonella as a Novel Anticancer Vector*, 57 CANCER RES. 4537-4544 (1997) (hereinafter "Pawelek").

E. Jirillo et al., *Relationship Between Immune System and Gram-Negative Bacteria. Acid-Treated Salmonella Minnesota R 595 (Re) Enhances Immune Responsiveness in Patients with Gynecologic Malignancies*, 8 INT. J. IMMUNOPHARMAC. 881-886 (1986) (hereinafter "Jirillo").

Appellants additionally rely on the following references:

KU Chow et al., *In AML cell lines Ara-C combined with purine analogues is able to exert synergistic as well as antagonistic effects on proliferation, apoptosis and disruption of mitochondrial membrane potential*, 44 LEUK. LYMPHOMA 165-173 (2003) (Abstract only) (hereinafter "Chow").

DR Budman et al., *Synergistic and antagonistic combinations of drugs in human prostate cancer cell lines in vitro*, 13 ANTICANCER DRUGS 1011-1016 (2002) (Abstract only) (hereafter "Budman").

Girija P. Dasmahapatra et al., *In vitro Combination Treatment with Perifosine and UCN-01 Demonstrates Synergism against Prostate (PC-3) and Lung (A549) Epithelial Adenocarcinoma Cell Lines*, 10 CLIN. CANCER RES. 5242-5252 (2004) (hereinafter "Dasmahapatra").

Alison G. Freifeld et al., *Fever in the Neutropenic Cancer Patient*, in CLINICAL ONCOLOGY, chap. 46, pp. 925-926 (3d ed. 2004) (hereinafter "Freifeld").

The claims on appeal stand rejected as follows:

Claims 113, 116, 117, 119, 120, 123, and 124 under 35 U.S.C. § 103(a) as obvious over Low in view of Schachter (Ans. 5); and

Claims 115, 121, and 122 under 35 U.S.C. § 103(a) as obvious over Low in view of Schachter and Pawelek (*id.* at 8).

ISSUE

With regard to each of claims 113, 115, and 123, the issue on appeal is: Does the evidence of record support the Examiner's conclusion that it would have been obvious to treat a solid tumor cancer with both a *Salmonella* msbB$^-$ mutant, as disclosed in Low, and cisplatin, as disclosed in Schachter?

FINDINGS OF FACT

FF1. We agree with the Examiner's explicit findings regarding the scope and content of the Low, Schachter, and Pawelek (Ans. 5-9).

FF2. For example, as found by the Examiner, Low discloses "that the *msbB*$^-$ bacteria can be safe for use in humans" (Low 40; Ans. 5-6).

FF3. Chow discloses that Ara-C combined with certain purine analogues "exhibited additive to antagonistic effects," but that the combination of Ara-C with another purine analogue "exclusively yielded synergistic effects" (Chow, Abstract).

FF4. Budman discloses that "[d]ocetaxel demonstrated cytotoxic additive effects or synergy" with certain drugs, but that other drugs, including cisplatin, carboplatin, or etoposide, "were antagonistic when combined with docetaxel." In particular, Budman states that

"[c]ombinations of docetaxel with platinum or etoposide may lead to subadditive effects in treatment." (Budman, Abstract.)

FF5. Dasmahapatra discloses that, at the concentrations used, perifosine and UCN-01 "did not significantly affect the growth of" two cancer cell lines, but that, "in combination at the same respective individual concentrations . . . , virtually complete growth inhibition of both the cell lines resulted" (Dasmahapatra, Abstract).

FF6. Freifeld discloses:

> Neutropenia is a common and predictable consequence of many cytotoxic cancer therapies. . . . [A] deficit of neutrophils (i.e., neutropenia) is associated with an increase in susceptibility to infections as well as an attenuation of inflammatory responses to infections. . . . Infection unopposed by innate neutrophil responses can progress rapidly and relentlessly, leading to high levels of morbidity and mortality.

(Freifeld 925.)

PRINCIPLES OF LAW

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen Inc. v. F. Hoffman-LA Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). However, "[o]bviousness does not require absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

ANALYSIS

We adopt the Examiner's reasoning and response to arguments as set forth in the Examiner's Answer as our own, except that we have not relied on Jirillo in reaching our decision. We provide the following additional comments with regard to arguments raised in the Reply Briefs.

Chow, Budman, and Dasmahapatra teach that a drug combination may be synergistic, additive, or antagonistic[4] (FF3-5). In addition, we agree that these references support Appellants' position that one of ordinary skill in the art would not be able to predict prior to testing a particular combination whether it will provide a synergistic, additive, or antagonistic effect. However, we do not agree that that degree of predictability is required. Instead, we find it sufficient to establish a prima facie case of obviousness that one of ordinary skill in the art would have been able to reasonably predict that the combination would be effective in treating cancer.

We recognize that "[n]eutropenia is a common and predictable consequence of many cytotoxic cancer therapies" (FF6). However, given the disclosure in Low "that the *msbB*$^-$ bacteria can be safe for use in humans" (FF2), we do not agree that the risk of neutropenia, assuming that

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[4] Appellants argue that the term antagonistic should be interpreted based on the second definition of the term "antagonism" in the Merriam-Webster online dictionary (2d Reply Br. 6). Based on the recited definition, the term "antagonistic" would include a result that is subadditive but not less than either drug alone. This interpretation appears to be consistent with how the term is being used in Budman, which alternately refers to the combination of docetaxel with etoposide as "antagonistic" or "subadditive" (FF4). Thus, we adopt this definition of the term.

this risk was known at the time of the invention,[5] is sufficient to overcome the prima facie case of obviousness.

With regard to the alleged evidence of synergism, we agree with the Examiner that it is not commensurate with the scope of the claims (Supp. Ans. 6). More importantly, it is not even directed to the elected species, which contains cisplatin (Ans. 4).

CONCLUSION

The evidence of record support the Examiner's conclusion that it would have been obvious to treat a solid tumor cancer with both a *Salmonella* msbB$^-$ mutant, as disclosed in Low, and cisplatin, as disclosed in Schachter. We therefore affirm the obviousness rejections of claims 113, 115, and 123. Claims 116, 117, 119, and 120 fall with claim 113; claims 121 and 122 fall with claim 115; and claim 124 falls with claim 123. 37 C.F.R. § 41.37(c)(1)(vii).

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

[5] Freifeld, which is relied upon by Appellants for teaching this, is not prior art as to the present application.

cdc

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